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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/816,467	03/26/2001	Laurent Coen	3495.0174-01	7062

22852 7590 06/04/2003

FINNEGAN, HENDERSON, FARABOW, GARRETT & DUNNER LLP
1300 I STREET, NW
WASHINGTON, DC 20005

EXAMINER	
CHEN, SHIN LIN	
ART UNIT	**PAPER NUMBER**
1632	

DATE MAILED: 06/04/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.	Applicant(s)
09/816,467	Coen et al.
Examiner	**Art Unit**
Shin-Lin Chen	1632

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *Apr 10, 2003*.

2a) ☒ This action is **FINAL.** 2b) ☐ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *1-19 and 21-35* is/are pending in the application.

4a) Of the above, claim(s) *1-16 and 24-33* is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *17-19, 21-23, 34, and 35* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Applicants' amendment filed 4-10-03 has been entered. Claims 17-19 and 23 have been amended. Claims 34 and 35 have been added. Claims 1-19 and 21-35 are pending and claims 17-19, 21-23, 34 and 35 are under consideration.

Double Patenting

1. A rejection based on double patenting of the "same invention" type finds its support in the language of 35 U.S.C. 101 which states that "whoever invents or discovers any new and useful process ... may obtain a patent therefor ..." (Emphasis added). Thus, the term "same invention," in this context, means an invention drawn to identical subject matter. See *Miller v. Eagle Mfg. Co.*, 151 U.S. 186 (1894); *In re Ockert*, 245 F.2d 467, 114 USPQ 330 (CCPA 1957); and *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970).

A statutory type (35 U.S.C. 101) double patenting rejection can be overcome by canceling or amending the conflicting claims so they are no longer coextensive in scope. The filing of a terminal disclaimer cannot overcome a double patenting rejection based upon 35 U.S.C. 101.

2. Claims 17 and 18 remain provisionally rejected under 35 U.S.C. 101 as claiming the same invention as that of claims 17 and 18 of copending Application No. 09/501,787. This is a provisional double patenting rejection since the conflicting claims have not in fact been patented. Applicants request Examiner to hold this rejection in abeyance until allowable subject matter has been indicated.

3. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

4. Claims 19 and 21-23 remain provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 19 and 21-23 of copending Application No. 09/501,787. Although the conflicting claims are not identical, they are not patentably distinct from each other because, although drawn to different scope, they encompass the same invention and obvious variants thereof. Applicants request Examiner to hold this rejection in abeyance until allowable subject matter has been indicated.

Claim Rejections - 35 USC § 112

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claim 19 remains rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention and is repeated for the reasons set forth in the preceding Official action mailed 12-18-02 (Paper No. 11). Applicant's arguments filed 4-10-03 have been fully considered but they are not persuasive.

Applicants argue that, structurally, the hybrid fragment comprises a fragment C and a fragment B and was well known in the art and, functionally, the variant fragment retains the capability of transferring *in vivo* a protein, a peptide, or a polynucleotide through a neuromuscular junction and at least a synapse. Applicants further argue that the common attribute of the claimed genus is derived from the structurally-define hybrid fragment of claim 17 (amendment, p. 6, 7). This is not found persuasive because of the reasons set forth in the preceding Official action mailed 12-18-02 (Paper No. 11). The hybrid fragment, comprising a fragment C and fragment B of TT, of claim 17 is just an example of the claimed genus but not common attribute of the claimed genus. "It is not enough for purposes of written description requirement of Section 112 that the disclosure, when combined with the knowledge in the art,

would lead one to speculate as to modification that the inventor might have envisioned, but failed to disclose." *Lockwood v. American Airlines Inc.* (Fed. Cir. March 1997) 41 USQP2d 1961 at 1966. The specification fails to provide the structural features of TTC or its variants that contributes to its activity of transferring a protein, a peptide, or a polynucleotide through a neuromuscular junction. There is no evidence of record that a particular region of amino acid residues within TTC is essential to its transferring activity. Structural features that could distinguish compounds in the genus from others in the protein or peptide class are missing from the disclosure. No common structural attributes identify the members of the genus. Therefore, the limited disclosed information is not sufficient to reasonably convey to one skilled in the art that applicants were in possession of the claimed amino acid variant fragments.

Applicants cite example 9 of USPTO written description guideline and argue the similarity between example 9 and the present claimed invention (amendment, p. 7-8). This is not found persuasive because of the reasons set forth in the preceding Official action mailed 12-18-02 (Paper No. 11) and the reasons set forth above. Example 9 deals with polynucleotide, however, the claimed invention is directed to amino acid variants. They are irrelevant to each other and each case has to be considered separately. Further, the example in the written description guideline is just an "example", it is not necessary that said example can be applied to every similar case to draw to the same conclusion.

7. Claim 19 remains rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a hybrid fragment of tetanus toxin, LacZ + TTC, as disclosed, does not reasonably provide enablement for any amino acid variant fragment having the same properties as said hybrid fragment. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims and is repeated for the reasons set forth in the preceding Official action mailed 12-18-02 (Paper No. 11). Applicant's arguments filed 4-10-03 have been fully considered but they are not persuasive.

Applicants argue that the specification need not disclose what is well-known in the art and already available to the public and the specification discloses how to make and use a functional TTC fragment, how to make variants or mutants, and how to screen said variants for the desired function. Applicants further argue that such screening is routine experimentation and no undue experimentation is required (amendment, p. 9-11). This is not found persuasive because of the reasons set forth in the preceding Official action mailed 12-18-02 (Paper No. 11). The claim encompasses a genus of numerous structural variants of TTC having the activity of transferring a protein, a peptide, or a polynucleotide through a neuromuscular junction. The specification fails to provide the structural features of TTC or its variants for its activity of transferring a protein, a peptide, or a polynucleotide through a neuromuscular junction. The specification also fails to provide adequate guidance and evidence how and which amino acid residue within TTC fragment can be deleted or substituted, or what amino acid residue can be

added to TTC fragment such that the resulting amino acid variant still retain the activity of TTC fragment as disclosed. It was known in the art that the amino acid sequence of a protein determines its structural and functional properties (including half-life), and the protein function was unpredictable at the time of the invention from mere amino acid sequence. Although is was known to make variants of a protein, however, characterization of a protein function from mere amino acid sequence was unpredictable and is not routine experimentation and the specification fails to provide sufficient enabling disclosure for the claimed genus of structural variants of TTC fragment. Thus, one skilled in the art at the time of the invention would require undue experimentation to practice over the full scope of the invention claimed.

Claim Rejections - 35 USC § 103

8. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later

invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

9. Claims 17-19 and 21-23 remain rejected and claims 34 and 35 are rejected under 35 U.S.C. 103(a) as being unpatentable over Mueller, 1994 (Report, ARO-27890.1-LS, Order No. AD-A290 501, NTIS, p. 1-15) in view of Hohne-Zell et al., 1993 FEBS Letters, Vol. 336, No. 1, p. 175-180 and is repeated for the reasons set forth in the preceding Official action mailed 12-18-02 (Paper No. 11). Applicant's arguments filed 4-10-03 have been fully considered but they are not persuasive.

Applicants argue that neither nor Hohne-Zell teaches or suggests a hybrid tetanus toxin fragment that includes fragment B or a fraction thereof having at least 11 amino acid residues (amendment, p. 12). This is not found persuasive because of the reasons set forth in the preceding Official action mailed 12-18-02 (Paper No. 11). Mueller teaches receptor mediated gene transfer in the central nervous system and "tetanus toxin is uniquely specific for uptake into neurons and enters the central nervous system from the circulation with the highest efficiency of any known protein" (e.g. p. 3). Tetanus toxin includes fragment B and fragment C, and contains at least 11 amino acid residues of fragmetn B. Thus, Mueller implies the use of tetanus toxin that includes fragment B and fragment C for receptor mediated gene transfer in the central nervous system. Hohne-Zell teaches zinc and the putative zinc-binding domain constitute the active site of the tetanus toxin light chain and replacement of histidine (position 233) by cysteine or valine and of glutamate (position 234) by glutamine completely abolished the activity of light chain on

calcium induced catecholamine release. Therefore, it would have been obvious for one of ordinary skill at the time of the invention to generate the claimed hybrid fragment or composition devoid of the zinc-binding domain to remove TT toxic activity for neuron specific gene transfer to central nervous system according to the collective teachings of Mueller and Hohne-Zell.

10. This application contains claims 1-16 and 24-33 drawn to an invention nonelected with traverse in Paper No. 10. A complete reply to the final rejection must include cancelation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

Conclusion

No claim is allowed.

11. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however,

will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Shin-Lin Chen whose telephone number is (703) 305-1678. The examiner can normally be reached on Monday to Friday from 9 am to 5:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah Reynolds can be reached on (703) 305-4051. The fax phone number for this group is (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist, whose telephone number is (703) 308-0196.

Shin-Lin Chen, Ph.D.